THE ACTION OF DIMETHYLTELLURIUM DIHALOIDS.

By the late DOUGLAS V. COW and W. E. DIXON.

(*From the Pharmacological Laboratory, Cambridge.*)

The internal administration of tellurium compounds has long been known to produce a garlic-like odour in the breath and from the skin; at one time this was commonly observed in those taking bismuth salts in which tellurium was apt to be an impurity. Reisert(1) found that ·0005 mgrm. TeO_2 taken by the mouth produced this odour in $1\frac{1}{4}$ hours and that it lasted some thirty hours; after taking 15 mgrms. the odour was still obvious after 237 days. Hofmeister(2) and his pupils proved that this odour was due to $Te(CH_3)_2$ and that in whatever form tellurium was administered the methyl compound could be detected in all parts of the body: dogs, rabbits, frogs, worms and crustacea can all bring about this change. Mead and Gies(3) showed that non-toxic doses of tellurium in various forms did not materially alter metabolism in dogs; large doses caused vomiting and later sleepiness, and toxic doses, after a period of restlessness, caused gradual paralysis and death from respiratory failure. Tellurium compounds (tellurates) may be regarded then as exerting little toxic action in higher animals, except when administered in very large doses, although certain bacteria are highly sensitive to them(4).

The present experiments were made with two isomeric dimethyltelluronium dichlorides $(CH_3)_2TeCl_2$ which were prepared in the Cambridge Chemical Laboratory by Dr R. H. Vernon(5). Both are quite stable and soluble in water, both the halogens are ionisable and can be precipitated quantitatively by silver nitrate. Dr Vernon suggests for these two isomerides the following formulæ which may be expressed in one plane.

Since in these simple compounds of quadrivalent tellurium two substances exist corresponding with one structural formula, it is clear that we are dealing with a new form of isomerism.

Apart from the action of tellurium we believed that an investigation of these compounds might afford some information on the relations between molecular structure and physiological action. The immediate action of these haloids, that is within a few hours, shows no likeness to what may be termed a tellurium action: they each cause a specific and different type of effect on tissues. It is only when they are broken down in the body and excreted as $Te(CH_3)_2$ that what is commonly regarded as a tellurium action comes into play. This change, however, begins almost immediately and is probably complete in a few hours, since the characteristic odour then becomes faint.

Our experiments were made upon cats, dogs and rabbits, and the effects are in broad outline the same in all animals. The animals were anæsthetised with A.C.E. and urethane unless otherwise stated.

Immediate effect of intravenous injection. The injection of 5 mgrms. of the β compound into the circulation of the cat or dog causes an immediate rise in the blood-pressure with increased frequency and depth of respiration. This effect lasts 20 to 30 seconds and the blood-pressure rapidly falls to normal. This is followed by a secondary rise which is usually more profound and always much more prolonged than the first effect (Fig. 1). When the whole action has passed off further injections may be made with similar results, but after each successive injection the effects become less pronounced: the initial stimulation of respiration and rise of blood-pressure become shorter, but the secondary rise in blood-pressure remains constant provided some three or four minutes are allowed to elapse between each injection.

The injection of 5 mgrms. of the α compound produces an entirely different type of effect: in the cat the heart immediately ceases to beat and the blood-pressure falls to zero. This does not usually last longer than 20–30 seconds, then the heart suddenly begins to beat again and the blood-pressure bounds up to a height above that before injection (Fig. 2). The effect is very similar to that obtained by injecting a concentrated solution of potassium chloride, and like the potassium effect it can be produced an indefinite number of times; unlike the β haloid the action of the α does not diminish with successive doses. Larger injections of the α haloid stop the heart-beat for a longer period and if sufficiently large cause death. The heart, however, does not appear to be permanently injured as it is not difficult to reestablish its activity with massage even after standstill for some minutes. Smaller doses of α induce a fall of blood-pressure lasting a minute or two without cessation of the heart-beat again simulating a potassium effect. Respiration is little influenced

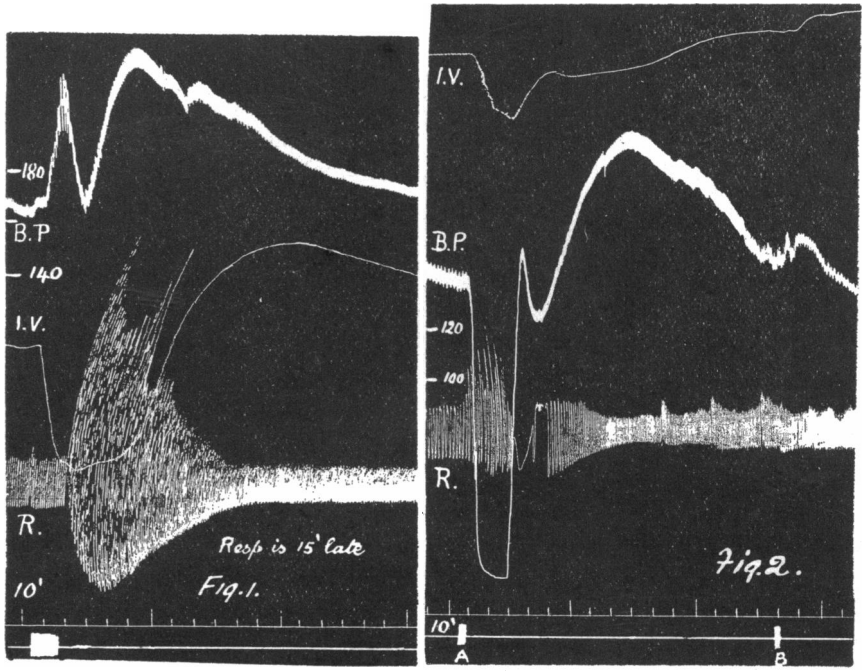

Fig. 1. Cat. Urethane. B.-P. Intestinal volume. Respiration. Injection 5 mgrms. β.

Fig. 2. Cat. Urethane. Intestinal volume. B.-P. Respiration. Injection at A 5 mgrms. of α: at B 1 mgrm. atropine.

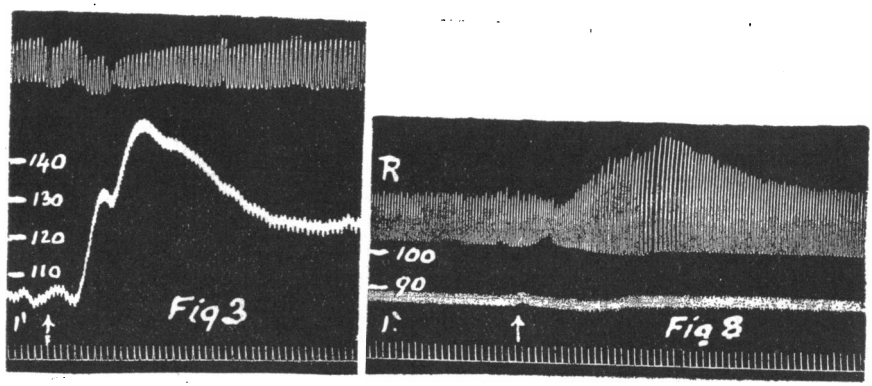

Fig. 3. Rabbit. Urethane. Respiration. B.-P. Injection 5 mgrms. β.

Fig. 8. Cat. Urethane. The animal had previously received 40 mgrms. β, and the vagi are paralysed but the motor nerves are intact. Shows effect of 5 mgrms. nicotine.

by the α compound: the immediate effect is no more than would be accounted for by the fall of blood-pressure.

The behaviour of the rabbit to the β compound is a little different from the cat and dog: only the secondary rise of blood-pressure occurs and in place of the first effect either no change is observed or a small and transient fall (Fig. 3).

Explanation of the vascular and respiratory effects. The primary rise in blood-pressure associated with the increased respiration which follows the injection of the β haloid suggests that the effect is central, due to stimulation of the medulla. If the spinal cord of an animal is severed below the medulla the primary rise of blood-pressure is almost or entirely deleted. Or if the central nervous system of an animal is completely paralysed by nicotine the β fails to produce any initial rise of pressure. This augmented pressure is mainly due to vaso-constriction and such constriction is easily shown by plethysmographic experiments in which a limb or loop of intestine is placed in an oncometer. The volume of the organ shrinks as the blood-pressure rises (Fig. 6). The vaso-constriction is certainly not peripheral for the reasons already given and because perfusion experiments on isolated organs show that the β compound never constricts vessels, that is diminishes the outflow from the vein, but rather tends to increase it.

The secondary rise in blood-pressure commences from 30–60 seconds after injection. It occurs in decerebrate animals and in animals in which the whole central nervous system has been paralysed by apocodeine or nicotine. This effect also is mainly due to vaso-constriction of peripheral origin but not due, for reasons already mentioned, to the direct action of the drug. This suggests that the β haloid may act on the suprarenal glands and that the rise of blood-pressure may be due to the liberation of adrenaline. If the suprarenal glands of an animal are ligatured and excised, the injection of β causes no secondary rise of blood-pressure (Fig. 4). Section of the two splanchnic nerves in the cat does not materially influence this secondary pressor action of the drug, although it usually cuts out almost completely the primary pressor action by separating the medulla from the splanchnic area. The β haloid does not excite any part of the nervous system directly, except the medulla (Fig. 5). For this reason we believe that it excites the suprarenal gland cells to activity directly and quite independently of the nerve-supply and suggest that it may be a useful substance with which to stimulate the gland for experimental purposes or to determine whether or no the gland is functioning. After repeated doses in quick succession the gland becomes

exhausted so that further injections produce little or no secondary pressor effect unless a rest is given when further injections again produce an

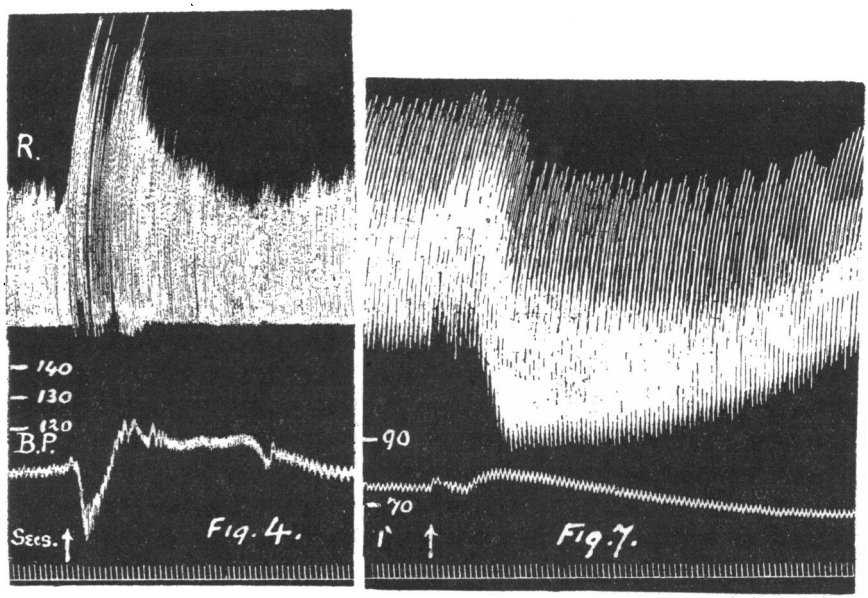

Fig. 4. Cat. Urethane. Splanchnics cut and both suprarenals ligatured off from the circulation. Injection 10 mgrms. β.

Fig. 7 Cat. Urethane. Cardiometer. B.-P. Shows an injection of 2 mgrms. β. The animal had already received 20 mgrms. β.

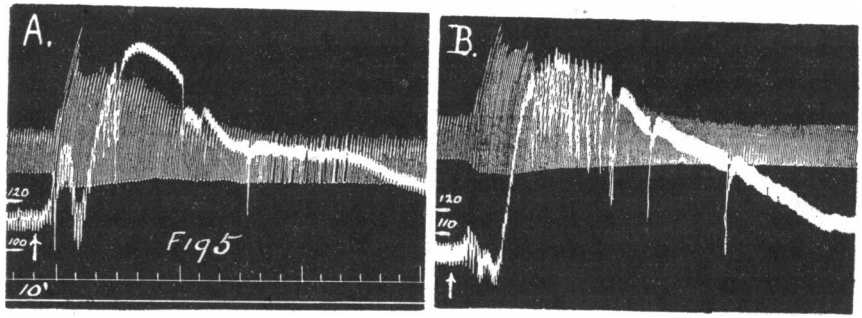

Fig. 5. Cat Urethane. *B* follows on *A*, but before *B* was taken the splanchnics were cut. Injection in each case 5 mgrms. β.

adrenaline action. We have endeavoured to verify this explanation by anæsthetising a cat slowly and quietly without undue excitement; one

suprarenal gland was then excised. The cat then received six intravenous injections of the β haloid, 60 mgrms. in all. Soon after the last injection the animal was killed and the second suprarenal gland excised. The two glands were weighed and made up into standard extracts with Ringer's solution and the activity of the extracts compared by testing their effects on isolated organs, rabbit's intestine and uterus, enucleated frog's eyes and on blood-pressure. Both extracts contained adrenaline however, although the larger amount was present in the extract of the gland first extirpated, but the difference was insignificant. This unexpected fact shows, if our explanation is valid, how rapidly the gland replaces the adrenaline it has lost.

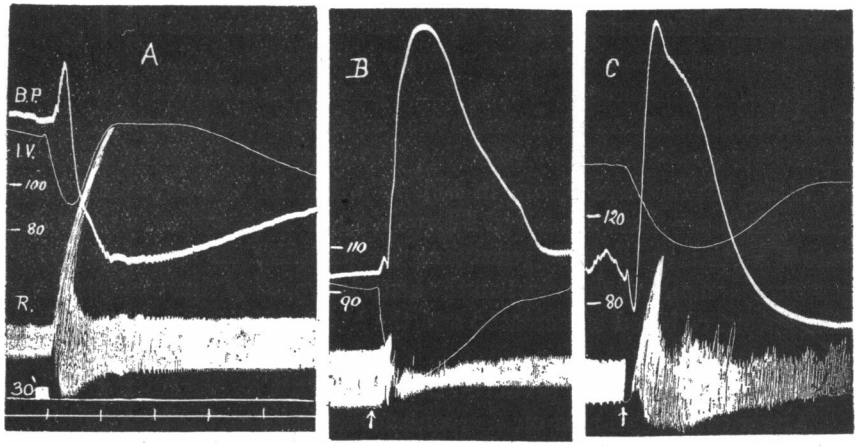

Fig. 6. Cat. Urethane. The intervals between *A* and *B* and *B* and *C* are four minutes. In *A* the fifth injection of β is shown (5 mgrms.). In *B* 5 mgrms. β injected. In *C* 5 mgrms. nicotine injected.

The depressor effect after repeated injections of β is shown in Fig. 6 *A*. This is apparently due to medullary depression which invariably follows profound medullary stimulation, but which after injections of β is generally masked by the pressor effect of adrenaline. The depressor effect is caused by vaso-dilatation. After a short rest of three or four minutes injections of the β haloid again cause a pressor effect from the liberation of adrenaline (Fig. 6 *B*); and there seems to be no limit to the amount of adrenaline which the suprarenal gland can manufacture provided a little time is given. An injection of nicotine is also shown in this figure to demonstrate the comparative effect between it and adrenaline (β) (Fig. 6 *C*). The respiratory curves in *B* and *C* are typical of

adrenaline and nicotine respectively, and the hump on the blood-pressure curve in *C* is also typical.

The depressor action of the α compound presents many similarities to that of potash compounds. If the heart of an animal is exposed when the haloid is injected, a few peristaltic-like waves can be seen to pass over the heart which then stops beating and becomes quiescent. Soon, however, the ventricles pass into a state of most intense fibrillation: if the dose has been too large this condition may not be observed unless the heart is gently massaged. The fibrillation generally lasts from two to five minutes and then, especially if aided by massage, passes off and the heart recovers completely. This effect is uninfluenced by the injection of atropine or calcium, and is caused by a direct action on the coordinating mechanism. The contractility of the ventricles returns a considerable time before auriculo-ventricular conductivity is complete.

Heart. From these effects on blood-pressure it is obvious that the β haloid should exert an adrenaline action on the heart in the second phase. This effect can be shown by recording the output of blood from the heart as in the cardiometer record in Fig. 7, p. 46. In this experiment the animal had previously received a large dose of urethane so as to obliterate the primary effect by paralysing the medulla: the action on blood-pressure is small but the effect on the heart is typical of that of adrenaline. The output of blood is increased and the heart empties itself more completely at each beat. This effect being the result of an action on the suprarenal glands is not produced in experiments on the isolated heart.

The α compound acts on the contractile tissue of the heart directly and causes standstill. If 5 mgrm. of α be injected into a lymph sac of a decerebrate frog arranged for recording the heart, the beat is first slowed in diastole, the height of contractions are slightly increased and death occurs in diastole a little after one hour: conduction is not altered. A like dose of the β compound injected under similar conditions first alters conduction; the A-V interval is increased, then the heart becomes irregular and later the ventricle contracts without reference to the auricles. Death occurs in diastole.

The introduction of 0·5 mgrm. of α into the coronary circulation of a surviving isolated rabbit's heart causes immediate ventricular standstill. The heart cannot be induced to beat again by the administration of calcium, atropine or adrenaline. Recovery may occur in time, but after the injection of 2 or 3 mgrms. the heart is killed, though the auricles continue to beat for some minutes.

The β compound produces a different type of effect. When the isolated

rabbit's heart is perfused with 1 in 50,000 β haloid it first beats a little more vigorously; after an hour, though still beating regularly, the tonus has risen considerably and in about two hours the heart dies in systole. Larger concentrations produce this effect in a shorter time. An analysis of the curves shows that in the later stages of poisoning heart-block is obtained just as in the frog, followed by complete auriculo-ventricular arrhythmia. Sometimes the right ventricle contracts alone and sometimes with the left ventricle. Death always occurs in systole. Hearts poisoned in this way respond in a normal manner to pilocarpine and atropine, but calcium, physostigmine and adrenaline exert little or no action.

Action on some surviving organs. The α haloids cause plain muscle throughout the body to contract: this effect is definite though never decided. The β compounds have no peripheral action on plain muscle of note and any slight effect there may be is never towards contraction. The following experiments from a number will exemplify this. The action on isolated blood vessels was determined by perfusing the surviving hind limbs and intestines of cats and rabbits, and measuring the outflow from the veins. The following is a typical experiment.

Cat. Cannula inserted into aorta and inferior vena cava just before bifurcation. Perfusion at body temperature with defibrinated blood from the same cat diluted with an equal quantity of Ringer's solution. Experiment performed in a warm oven at 80 mm. mercury pressure. The figures represent the times in seconds for the collection of 10 c.c. from the vein.

	Drug given	
30, 30, 28, 30,	α	32, 32, 25, 26, 25
36, 34, 34, 34,	β	32, 30, 32, 33

In each case 5 mgrms. of drug were injected into the tube connected with the artery.

The effect is trifling, but in every instance the α produces an initial constriction followed by dilatation.

On the uterus of the rat, guinea pig or rabbit this effect of α haloid is seen in a more decided form. The following is a typical experiment.

One horn of uterus of guinea pig suspended in 100 c.c. of oxygenated Ringer's solution at 38° C. The uterus is fixed below and attached to a lever suitably weighted so as to record on a smoked surface. The addition of 10 mgrms. 1 p.c. α is without effect. The addition of 10 mgrms. 1 p.c. β causes maximal contraction.

The same type of effects can be seen on the isolated intestine. These experiments were performed with both longitudinal and circular strips of rabbit's intestine and under conditions identical with those on the uterus. The addition of 5 mgrms. α slightly increased the intestinal tone and decidedly increased the contractions of the automatic movements. The β produced no effect.

Action on the pituitary gland. Since the haloid exerts this powerful action on the suprarenal glands, its effect on the pituitary body was investigated. A dog was anæsthetised with urethane and morphine, and a cannula placed in the subcerebellar cisterna. The secretion of cerebro-spinal fluid was collected. We have found (unpublished paper) that the normal secretion of the posterior part of the pituitary is *via* the cerebro-spinal fluid and that certain substances increase this secretion. The amount of pituitary in 1 c.c. of cerebro-spinal fluid can be assayed with some degree of accuracy by comparing it with a standard pituitary solution on the isolated uterus of the guinea pig. In two experiments the administration of the β haloid, even in large doses such as 50 mgrms. was entirely without effect on the pituitary secretion during a period of two hours.

Effect of large doses. If 60 mgrms. of α haloid be injected intravenously into an anæsthetised cat or rabbit, or 180–200 mgrms. into a dog of 12 kilos., no immediate poisonous effects are produced, provided that the drug is injected so slowly that the heart is not sent into fibrillary twitchings. All the nervous structures central and peripheral remain intact, and the only decided effect is a general tendency for plain muscle throughout the body to contract.

The β haloid behaves differently when injected in similar doses. First, it paralyses sympathetic ganglion cells throughout the body; after considerably larger doses the cranio-sacral autonomic nerve cells are paralysed and later the spinal cord and medulla: finally, the motor nerve endings and all nerve structures are paralysed. The injection of 60 mgrms. into a cat will paralyse the vagus, splanchnics, cervical sympathetic and chorda tympani nerves, though if the electrodes are placed on the post-ganglionic fibres in the case of the last three nerves typical effects of stimulation are observed. The paralysis is therefore situated in the nerve-cells. The relative effect of the α and β compounds can be seen by painting the superior cervical ganglion of a cat on the one side with 1 per cent. α haloid and on the other with 0·1 per cent. β haloid. The β causes paralysis in two or three minutes; the α is without action.

It is interesting to note that injections of β haloids paralyse the sympathetic ganglion cells throughout the body at a time when the medullary centres including the respiratory are still intact. At this stage of the action of the β haloid nicotine causes no vaso-constriction, intestinal inhibition nor rise in blood-pressure, but it produced decided stimulation of respiration (Fig. 8, p. 44). Other drugs, however, which act more peripherally than nicotine, such as arecoline and adrenaline,

produce their normal type of action. Slightly larger doses paralyse the whole central nervous system; at this stage strychnine loses its convulsant action; a little later and the motor nerves also no longer respond to electrical stimulation by contraction of muscle. The rabbit is more resistant to the narcotising action of the β and larger doses may be required to produce the full effect.

Excretion. Both these tellurium compounds are broken up in the body into $Te(CH_3)_2$, in which form they are excreted mainly by the lungs. We demonstrated this with both substances in the rabbit. The animals were anæsthetised with urethane, and the trachea was connected with a metal tube which bifurcated, each bifurcation being provided with a valve, the one only allowing inlet of air and the other exit. The expiratory tube was connected with a Wolff's bottle containing chloroform so that the expired air bubbled through the liquid. The drug α or β was now slowly injected into a vein until 30 mgrms. had been administered at the end of an hour. The chloroform was then examined by Dr Vernon and found to contain an appreciable amount of $Te(CH_3)_2$, though it could not be estimated. Similar injections of the α and β compounds produced apparently an equal amount of this product. The urine was found to contain very little.

The activity of these compounds is not due to the methyl telluride since the intravenous injection of this substance, which possesses such an intense and clinging smell, is without any immediate physiological action.

Dr Vernon showed that the position of the methyl groups in methyl telluride must be the same as their position in the α dihaloids, because methyl telluride unites directly with the halogens according to the equation

$$Te(CH_3)_2 + Cl_2 = Te(CH_3)_2Cl_2,$$

giving the α dihaloids, never the β. Nevertheless it is unlikely that methyl telluride occurs in the tissues to any extent, since it dissolves slowly in water, being converted to the α base $Te(CH_3)_2(OH)_2$. The fact that emulsions of methyl telluride in water are without any decided action is in agreement with the relative inactivity of the α haloids.

The β haloids are less stable than the α. In water both haloids readily ionise and, as the action of the two is entirely different and commences as soon as the drug reaches the circulation, we must assume an ionic action. The α compound is relatively inactive; the β is a pronounced narcotic and has a highly specific action on the suprarenals. Yet the positive ions of these two haloids are apparently the same and both carry

the same electrical charge. The physiological action cannot therefore be due to the elements of the positive ion, nor yet to its electrons, since these are the same in both compounds, but to some other factor, that is the strained condition when the haloids are arranged in the *cis* position. Here then we have a clear case of a compound in which neither the elements composing the compound nor their crude arrangement in the molecule determine the physiological action. The highly specific action of the β compound must be regarded as due to some energy factor which holds the constituents of the molecule in an abnormal and strained position.

Conclusions.

1. Two tellurium dimethyl dihaloids are described, having the same structural formula but entirely different actions, though both are excreted in the breath as methyl telluride.

2. The α haloid arranged in the *trans* position is relatively inactive.

3. The β haloid arranged in the *cis* position acts as a powerful medullary stimulant and specifically excites the suprarenal glands. Large doses paralyse nerve structures in the following order: (*a*) sympathetic ganglion cells, (*b*) other autonomic ganglion cells, (*c*) medulla and motor nerve endings.

4. The suprarenal gland can manufacture almost unlimited amounts of adrenaline.

5. The physiological activity of the β haloid is due to intramolecular strain.

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